<u>What Is Claimed Is</u>:

1. A protease inhibitor comprising the sequence:

X^1-Val-Cys-Ser-Glu-Gln-Ala-Glu-X^2-Gly-X^3-Cys-Arg-Ala-X^4-X^5-X^6-X^7-Trp-Tyr-Phe-Asp-Val-Thr-Glu-Gly-Lys-Cys-Ala-Pro-Phe-X^8-Tyr-Gly-Gly-Cys-X^9-X^{10}-X^{11}-X^{12}-Asn-Asn-Phe-Asp-Thr-Glu-Glu-Tyr-Cys-Met-Ala-Val-Cys-Gly-Ser-Ala-Ile,

wherein:

X^1 is selected from Glu-Val-Val-Arg-Glu-, Asp, or Glu;

X^2 is selected from Thr, Val, Ile and Ser;

X^3 is selected from Pro and Ala;

X^4 is selected from Arg, Ala, Leu, Gly, or Met;

X^5 is selected from Ile, His, Leu, Lys, Ala, or Phe;

X^6 is selected from Ser, Ile, Pro, Phe, Tyr, Trp, Asn, Leu, His, Lys, or Glu;

X^7 is selected from Arg, His, or Ala;

X^8 is selected from Phe, Val, Leu, or Gly;

X^9 is selected from Gly, Ala, Lys, Pro, Arg, Leu, Met, or Tyr;

X^{10} is selected from Ala, Arg, or Gly;

X^{11} is selected from Lys, Ala, or Asn;

X^{12} is selected from Ser, Ala, or Arg;

provided that:

when X^4 is Arg, X^6 is Ile;

when X^9 is Arg, X^4 is Ala or Leu; when X^9 is Tyr, X^4 is Ala or X^5 is His; and

either X^5 is not Ile; or X^6 is not Ser; or X^9 is not Leu, Phe, Met, Tyr, or Asn; or X^{10} is not Gly; or X^{11} is not Asn; or X^{12} is not Arg.

2. A protease inhibitor comprising the sequence:

X^1-Val-Cys-Ser-Glu-Gln-Ala-Glu-Thr-Gly-Pro-Cys-Arg-Ala-X^2-X^3-X^4-Arg-Trp-Tyr-Phe-Asp-Val-Thr-Glu-Gly-Lys-Cys-Ala-Pro-Phe-Phe-Tyr-Gly-Gly-Cys-X^5-Gly-Asn-Arg-Asn-

Asn-Phe-Asp-Thr-Glu-Glu-Tyr-Cys-Met-Ala-
Val-Cys-Gly-Ser-Ala-Ile,

wherein:

X^1 is selected from Glu-Val-Val-Arg-Glu-, Asp, or Glu;

X^2 is selected from Ala, Leu, Gly, or Met;

X^3 is selected from Ile, His, Leu, Lys, Ala, or Phe;

X^4 is selected from Ser, Ile, Pro, Phe, Tyr, Trp, Asn, Leu, His, Lys, or Glu;

X^5 is selected from Gly, Ala, Lys, Pro, Arg, Leu, Met, or Tyr;

provided that:

when X^5 is Arg, X^2 is Ala or Leu; when X^5 is Tyr, X^2 is Ala or X^3 is His; and

either X^3 is not Ile; or X^4 is not Ser; or X^5 is not Leu, Phe, Met, Tyr, or Asn.

3. A protease inhibitor comprising the sequence:

Glu-Val-Val-Arg-Glu-Val-Cys-Ser-Glu-Gln-
Ala-Glu-Thr-Gly-Pro-Cys-Arg-Ala-X^1-X^2-X^3-
Arg-Trp-Tyr-Phe-Asp-Val-Thr-Glu-Gly-Lys-
Cys-Ala-Pro-Phe-Phe-Tyr-Gly-Gly-Cys-X^4-
Gly-Asn-Arg-Asn-Asn-Phe-Asp-Thr-Glu-Glu-
Tyr-Cys-Met-Ala-Val-Cys-Gly-Ser-Ala-Ile,

wherein:

X^1 is selected from Ala, Leu, Gly, or Met;

X^2 is selected from Ile, His, Leu, Lys, Ala, or Phe;

X^3 is selected from Ser, Ile, Pro, Phe, Tyr, Trp, Asn, Leu, His, Lys, or Glu;

X^4 is selected from Gly, Arg, Leu, Met, or Tyr;

provided that:

when X^1 is Ala, X^2 is Ile, His, or Leu;

when X^1 is Leu, X^2 is Ile or His;

when X^1 is Leu and X^2 is Ile, X^3 is not Ser;

when X^1 is Gly, X^2 is Ile;

when X^4 is Arg, X^1 is Ala or Leu;

when X^4 is Tyr, X^1 is Ala or X^2 is His; and

either X^1 is not Met, or X^2 is not Ile, or X^3 is not Ser, or X^4 is not Gly.

4. A protease inhibitor according to claim 1, wherein at least two amino acid residues selected from the group consisting of X^4, X^5, X^6, and X^7 differ from the residues found in the naturally occurring sequence of KPI.

5. A protease inhibitor according to claim 1, wherein X^1 is Asp or Glu, X^2 is Thr, X^3 is Pro, and X^{12} is Ser.

6. A protease inhibitor according to claim 5, wherein X^1 is Glu, X^2 is Thr, X^3 is Pro, X^4 is Met, X^5 is Ile, X^6 is Ser, X^7 is Arg, x^8 is Phe, X^9 is Gly, X^{10} is Gly, and X^{11} is Asn.

7. A protease inhibitor according to claim 5, wherein X^1 is Asp, X^2 is Thr, X^3 is Pro, X^4 is Arg, X^5 is Ile, X^6 is Ile, X^7 is Arg, x^8 is Val, X^9 is Arg, X^{10} is Ala, and X^{11} is Lys.

8. A protease inhibitor according to claim 1, wherein X^1 is Glu-Val-Val-Arg-Glu-, X^2 is Thr, X^3 is Pro, X^4 is Met, X^5 is Ile, X^6 is Ser, X^7 is Arg, x^8 is Phe, X^9 is Gly, X^{10} is Gly, X^{11} is Asn, and X^{12} is Ala.

9. A protease inhibitor according to claim 1, wherein X^1 is Glu-Val-Val-Arg-Glu-, X^2 is Thr, X^3 is Pro, X^4 is Met, X^5 is Ile, X^6 is Ser, X^7 is Arg, x^8 is Phe, X^9 is Gly, X^{10} is Gly, X^{11} is Ala, and X^{12} is Arg.

10. A protease inhibitor according to claim 1, wherein X^1 is Glu, X^2 is Thr, X^3 is Pro, X^4 is Met, X^5 is Ile, X^6 is Ser, X^7 is Arg, x^8 is Phe, X^9 is Gly, X^{10} is Ala, X^{11} is Asn, and X^{12} is Arg.

11. A protease inhibitor according to claim 1, wherein X^1 is Glu-Val-Val-Arg-Glu-, X^2 is Thr, X^3 is Pro, X^4 is Met, X^5 is Ile, X^6 is Ser, X^7 is Arg, x^8 is Phe, X^9 is Gly, X^{10} is Arg, X^{11} is Asn, and X^{12} is Arg.

12. A protease inhibitor according to claim 1, wherein X^1 is Glu-Val-Val-Arg-Glu-, X^2 is Thr, X^3 is Pro, X^4 is Met, X^5 is Ile, X^6 is Ser, X^7 is Arg, x^8 is Val, Leu, or Gly, X^9 is Gly, X^{10} is Gly, X^{11} is Asn, and X^{12} is Arg.

13. A protease inhibitor according to claim 1, wherein X^1 is Glu-Val-Val-Arg-Glu-, X^2 is Thr, X^3 is Pro, X^4 is Met, X^5 is Ile, X^6 is Ser, X^7 is Ala, x^8 is Phe, X^9 is Gly, X^{10} is Gly, X^{11} is Asn, and X^{12} is Arg.

14. A protease inhibitor according to claim 1, wherein X^1 is Glu-Val-Val-Arg-Glu-, X^2 is Thr, Val, or Ser, X^3 is Pro, X^4 is Ala or Leu, X^5 is Ile, X^6 is Tyr, X^7 His, X^8 is Phe, X^9 is Gly, X^{10} is Gly, X^{11} is Ala, and X^{12} is Arg.

15. A protease inhibitor according to claim 14, wherein X^2 is Thr, and X^4 is Ala.

16. A protease inhibitor according to claim 14, wherein X^2 is Thr, and X^4 is Leu.

17. A protease inhibitor according to claim 14, wherein X^2 is Val, and X^4 is Ala.

18. A protease inhibitor according to claim 14, wherein X^2 is Ser, and X^4 is Ala.

19. A protease inhibitor according to claim 14, wherein X^2 is Val, and X^4 is Leu.

20. A protease inhibitor according to claim 14, wherein X^2 is Ser, and X^4 is Leu.

21. A protease inhibitor according to claim 1, wherein X^1 is Glu-Val-Val-Arg-Glu-, X^2 is Thr, X^3 is Pro, X^4 is Leu, X^5 is Phe, X^6 is Lys, X^7 is Arg, X^8 is Phe, X^9 is Gly, X^{10} is Gly, X^{11} is Ala, and X^{12} is Arg.

22. A protease inhibitor according to claim 1, wherein X^1 is Glu-Val-Val-Arg-Glu-, X^2 is Thr, X^3 is Pro, X^4 is Leu, X^5 is Phe, X^6 is Lys, X^7 is Arg, X^8 is Phe, X^9 is Tyr, X^{10} is Gly, X^{11} is Ala, and X^{12} is Arg.

23. A protease inhibitor according to claim 1, wherein X^1 is Glu-Val-Val-Arg-Glu-, X^2 is Thr, X^3 is Pro, X^4 is Leu, X^5 is Phe, X^6 is Lys, X^7 is Arg, X^8 is Phe, X^9 is Leu, X^{10} is Gly, X^{11} is Ala, and X^{12} is Arg.

24. A protease inhibitor according to claim 2, wherein X^1 is Glu, X^2 is Met, X^3 is Ile, X^4 is Ile, and X^5 is Gly.

25. A protease inhibitor according to claim 3, wherein X^1 is Met, X^3 is Ser, and X^4 is Gly.

26. A protease inhibitor according to claim 25, wherein X^2 is selected from His, Ala, Phe, Lys, and Leu.

27. A protease inhibitor according to claim 26, wherein X^2 is His.

28. A protease inhibitor according to claim 27, wherein X^2 is Ala.

29. A protease inhibitor according to claim 27, wherein X^2 is Phe.

30. A protease inhibitor according to claim 27, wherein X^2 is Lys.

31. A protease inhibitor according to claim 27, wherein X^2 is Leu.

32. A protease inhibitor according to claim 3, wherein X^1 is Met, X^2 is Ile, and X^4 is Gly.

33. A protease inhibitor according to claim 32, wherein X^3 is Ile.

34. A protease inhibitor according to claim 32, wherein X^3 is Pro.

35. A protease inhibitor according to claim 32, wherein X^3 is Phe.

36. A protease inhibitor according to claim 32, wherein X^3 is Tyr.

37. A protease inhibitor according to claim 32, wherein X^3 is Trp.

38. A protease inhibitor according to claim 32, wherein X^3 is Asn.

39. A protease inhibitor according to claim 32, wherein X^3 is Leu.

40. A protease inhibitor according to claim 32, wherein X^3 is Lys.

41. A protease inhibitor according to claim 32, wherein X^3 is His.

42. A protease inhibitor according to claim 32, wherein X^3 is Glu.

43. A protease inhibitor according to claim 3, wherein X^1 is Ala.

44. A protease inhibitor according to claim 43, wherein X^2 is Ile.

45. A protease inhibitor according to claim 44, wherein X^3 is Phe, and X^4 is Gly.

46. A protease inhibitor according to claim 44, wherein X^3 is Tyr, and X^4 is Gly.

47. A protease inhibitor according to claim 44, wherein X^3 is Trp, and X^4 is Gly.

48. A protease inhibitor according to claim 44, wherein X^3 is Ser or Phe, and X^4 is Arg or Tyr.

49. A protease inhibitor according to claim 43, wherein X^2 is His or Leu, X^3 is Phe, and X^4 is Gly.

50. A protease inhibitor according to claim 3, wherein X^1 is Leu.

51. A protease inhibitor according to claim 50, wherein X^2 is His, X^3 is Asn or Phe, and X^4 is Gly.

52. A protease inhibitor according to claim 50, wherein X^2 is Ile, X^3 is Pro, and X^4 is Gly.

53. A protease inhibitor according to claim 3, wherein X^1 is Gly, X^2 is Ile, X^3 is Tyr, and X^4 is Gly.

54. A protease inhibitor according to claim 3, wherein X^1 is Met, X^2 is His, X^3 is Ser, and X^4 is Tyr.

55. An isolated DNA molecule comprising a DNA sequence encoding a protease inhibitor according to claim 1.

56. An isolated DNA molecule according to claim 55, operably linked to a regulatory sequence that controls expression of the coding sequence in a host cell.

57. An isolated DNA molecule according to claim 56, further comprising a DNA sequence encoding a secretory signal peptide.

58. An isolated DNA molecule according to claim 57, wherein said secretory signal peptide comprises the signal sequence of yeast alpha-mating factor.

59. A host cell transformed with a DNA molecule according to claim 55.

60. A host cell according to claim 59, wherein said host cell is *E. coli* or a yeast cell.

61. A host cell according to claim 60, wherein said host cell is *Saccharomyces cerevisiae*.

62. A method for producing a protease inhibitor, comprising the steps of culturing a host cell according to claim 59 and isolating and purifying said protease inhibitor.

63. A pharmaceutical composition, comprising a protease inhibitor according to claim 1, together with a pharmaceutically acceptable sterile vehicle.

64. A method of treatment of a clinical condition associated with increased activity of one or more serine proteases, comprising administering to a patient suffering from said clinical condition an effective amount of a pharmaceutical composition according to claim 63.

65. The method of treatment of claim 64, wherein said clinical condition is blood loss during surgery.

66. A method for inhibiting the activity of serine proteases of interest in a mammal comprising administering a therapeutically effective dose of a pharmaceutical composition according to claim 63.

67. The method of claim 66, wherein said serine proteases are selected from the group consisting of:

kallikrein; chymotrypsins A and B; trypsin; elastase; subtilisin; coagulants and procoagulants, particularly those in active form, including coagulation factors such as factors VIIa, IXa, Xa, XIa, and XIIa; plasmin; thrombin; proteinase-3; enterokinase; acrosin; cathepsin; urokinase; and tissue plasminogen activator.

68. A protease inhibitor comprising the sequence:

X^1-Val-Cys-Ser-Glu-Gln-Ala-Glu-X^2-Gly-Pro-Cys-Arg-Ala-X^3-X^4-X^5-X^6-Arg-Trp-Tyr-Phe-Asp-Val-Thr-Glu-Gly-Lys-Cys-Ala-Pro-Phe-Phe-Tyr-Gly-Gly-Cys-X^7-Gly-Asn-Arg-Asn-Asn-Phe-Asp-Thr-Glu-Glu-Tyr-Cys-Met-Ala-Val-Cys-Gly-Ser-Ala-Ile,

wherein:

X^1 is selected from Glu-Val-Val-Arg-Glu-, Asp, or Glu;

X^2 is selected from Thr, Val, Ile and Ser;

X^3 is selected from Arg, Ala, Leu, Gly, or Met;

X^4 is selected from Ile, His, Leu, Lys, Ala, or Phe;

X^5 is selected from Ser, Ile, Pro, Phe, Tyr, Trp, Asn, Leu, His, Lys, or Glu;

X^6 is selected from Arg, His, or Ala; and

X^7 is selected from Gly, Ala, Lys, Pro, Arg, Leu, Met, or Tyr.

69. A protease inhibitor according to claim 68, wherein at least two amino acid residues selected from the group consisting of X^3, X^4, X^5, and X^6 differ from the residues found in the naturally occurring sequence of KPI.

70. A protease inhibitor according to claim 68, wherein X^1 is Glu-Val-Val-Arg-Glu-, X^2 is Thr, Val, or Ser, X^3 is Ala or Leu, X^4 is Ile, X^5 is Tyr, X^6 is His and X^7 is Gly.

71. A protease inhibitor according to claim 70, wherein X^2 is Thr, and X^3 is Ala.

72. A protease inhibitor according to claim 70, wherein X^2 is Thr, and X^3 is Leu.

73. A protease inhibitor according to claim 70, wherein X^2 is Val, and X^3 is Ala.

74. A protease inhibitor according to claim 70, wherein X^2 is Ser, and X^3 is Ala.

75. A protease inhibitor according to claim 70, wherein X^2 is Val, and X^3 is Leu.

76. A protease inhibitor according to claim 70, wherein X^2 is Ser, and X^3 is Leu.

77. A protease inhibitor according to claim 68, wherein X^1 is Glu-Val-Val-Arg-Glu-, X^2 is Thr, X^3 is Leu, X^4 is Phe, X^5 is Lys, X^6 is Arg and X^7 is Gly.

78. A protease inhibitor according to claim 68, wherein X^1 is Glu-Val-Val-Arg-Glu-, X^2 is Thr, X^3 is Leu, X^4 is Phe, X^5 is Lys, X^6 is Arg and X^7 is Tyr.

79. A protease inhibitor according to claim 68, wherein X^1 is Glu-Val-Val-Arg-Glu-, X^2 is Thr, X^3 is Leu, X^4 is Phe, X^5 is Lys, X^6 is Arg and X^7 is Leu.